OBJECTIVES

Large familial papillary thyroid carcinoma (PTC) in childhood has been described only in single cases, mainly in the context of rare syndromes (e.g. APC-associated-syndrome, PTEN-hamartoma syndromes). Small PTC in Graves’ disease (GD) has been described in adults, but not in familial cases including young children. PTC in GD seems to be more aggressive. We investigated the association of large metastatic PTC in a 10 years old girl and her mother evolving rapidly in both of them after the manifestation of GD. A genetic basis for the non-syndromic familial GD and PTC in a background with a high prevalence of PTC in adults GD was suspected.

Patient History

The mother:
- Manifestation Graves disease (TSH-R AB positive) 2014: initiation of antithyroid drug treatment with carbimazole
- 3 months later:
  - detection of a large nodule, PTC, one LN metastasis,
  - ablative thyroid surgery, radioidine treatment

The patient:
- Manifestation Graves disease (TSH-R AB positive) 2015:
  - loss of 10 kg BW
  - tachycardia
  - prominent eyes
- initiation of antithyroid drug treatment with carbimazole
- 3 months later:
  - detection of a large nodule, PTC, one LN metastasis,
  - ablative thyroid surgery, radioidine treatment

Results

Imaging studies:
The ultrasound studies revealed a 1.2 x 2.3 cm large nodule in the right lobe and the thyroid with an esochostructure compatible with autoimmune thyroid disease and increased perfusion. (Fig 1/2/3) Scintigraphy revealed an increased uptake (Fig 4), thus the nodule was not visible.

Histopathology:
16 mm PTC with several lymph node metastases (pT1bN1b(9/10)R0L0V0) in a thyroid with chronic interstitial inflammation

Genetic studies:
No somatic variants were found for APC 1-16; DDR2 15; DICER1 1-8; EGFR 18-21; ERBBB 5,6,15,20,23,29; FGFR1,3,7, 13, 17, 18; HRAS 2-4; KIT 9-11, 13, 17, 18; KRAS 2-4; MET 3, 8, 11, 14, 19; NRAS 2; PDGFR 12, 14, 18; PIK3CA 3, 5, 10, 16, 21; PRKAR1A 1-11, PTEN 1-9; RAF/11; RET 0, 11, 13-16; TP53 4-9;

Variants:
1. BRAF-Mutation (V600E)
2. TSH-R Exon 1 mutation: rs2239610 c.154C>A p.Pro52Thr

Conclusions

A rare association of GD and PTC in a mother and her daughter was associated with BRAF V600E in the tumor tissue. A TSH-receptor variant in Exon 1 was found also in the two sisters with cystic abnormalities in ultrasound studies. Since a high prevalence of PTC associated with GD is known in the ethnic background of the family, a further genetic work-up has been initiated, to find out if this rare association could be caused by a genetic predisposition in thyroid structure or function. Alternatively an expression of a microRNA caused by an increase in proliferation, by a genetic variant of the immune system, an environmental factor or the antithyroid drug treatment may have triggered the development of the PTC.

References